REMARKS

Claims 1-6, 8-12 and 16-42 are pending in the application. Claim 43 has been added. The claim is supported throughout the specification, for example in paragraph 8 of the application as published. No new matter has been added.

Rejection of claims under 35 U.S.C. §103

Claims 1-6 and 8-12 and 15-42 were rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Ueno (US Patent 6,566,398) and Yano et al. (J. Nutrition. 130:1095-1101, 2000) in view of Troyer et al. (US Patent 6,506,412) and Schneider et al. (US Patent 6,353,022). This rejection is respectfully traversed.

The claims are drawn to methods of treatment of dry eye, meibomian gland inflammation, meibomian gland dysfunction, and dry mouth using a nutritional supplement containing an n-3 rich oil and an n-6 fatty acid containing oil; the nutritional supplement; and methods of manufacturing the nutritional supplement for the treatment. In the claimed supplement, the n-3 rich oil provides a high dose of each EPA (150-500 mg) and DHA (50-500 mg) providing a total of ***at least 200-1000 mg of omega-3 fatty acids***, and the ratio of the weight of the n-6 fatty acid containing oil to the n-3 rich oil is about 1 to 3 to about 3 to 1. In certain embodiments, narrower ranges of EPA and DHA levels are provided including 350 mg-450 mg of EPA and 250-350 mg of DHA, providing a total of ***at least 600-800 mg of omega-3 fatty acids***. Further, some of the claimed nutritional supplements of the instantly claimed invention include 1 g of an oil rich in omega-6 fatty acids, further increasing the amount of fatty acid provided. In certain embodiments, the supplement includes an ***oil soluble*** antioxidant such as vitamin E. Claims are directed to more specific formulas consisting essentially of specific combinations of the components of the instant claims.

Applicant submits that the rejection does not take into consideration the teachings of each of the cited references as a whole. In discussing what each reference teaches as a whole, Applicant is not arguing against the references

individually, but instead pointing out specific teachings of each reference as reasons that the references cannot be combined, either due to contradictions between the references, or that the combination of references would not lead one to arrive at the instantly claimed invention.

The Court has addressed the issue of obviousness in chemical cases since the decision of KSR. Specifically the court stated:

> While the KSR Court rejected a rigid application of the... TSM test in an obviousness inquiry, ***the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does'*** in an obviousness determination.
>
> When there is a design need or market pressure to solve a problem and there is a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, ***the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation***. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. *Takeda Chemical Industries Ltd. v. Alphapharm* Pty. 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The Federal Circuit in applying *KSR* noted that the TSM test need not be strictly applied, ***but that the need for a reason to combine the elements taught by the prior art remains***. In the instant case, one of the cited references taught administration of relatively high doses as contrary to the other reference which taught very low doses. The reference that taught low doses taught that the higher doses produced unwanted side effects. Applicant submits that there can be no motivation to combine the elements as claimed. If anything, the art is understood to teach away from the asserted obvious combination of the references.

The Office Action states that

> The combination of the relied upon references clearly teach that omega-3 fatty acids and omega-6 fatty acids individually (Ueno et al.) or in combination (Troyer et al.) have been previously used for the treatment of dry eye syndrome.

The instantly claimed invention includes limitations directed to both the components in the nutritional supplement and ***the amount of the components in the nutritional supplement***. As noted above, the amounts of EPA and DHA to be administered are relatively high.

In looking to Ueno and Troyer for insight in relation to dosages for administration, one finds starkly conflicting information.

The Office Action states that Troyer "teaches 500 mg daily dose of omega-3 fatty acids. In claim 14, Troyer teaches the combination of fatty acids at 235 mg, which is within the scope of the claimed invention." ***The 235 mg of fatty acids provided in Troyer include omega-3 fatty acid, omega-6 fatty acid, and GLA together***. This is clearly distinct from the instantly claimed invention which includes administration of 200-1000 mg, or in some claims 600-800 mg of omega-3 fatty acids alone. As the amount of omega-6 fatty acids must be at least 1/3 of the amount of omega-3 fatty acids, the minimum amount of fatty acids in the formulation would be 267 mg, which is clearly in excel of the amount taught by Troyer, and an amount that would be contrary to the teachings of Ueno.

The Office Action does not consider the doses taught by Ueno as they cannot be reconciled with the doses taught by Troyer. First, Ueno teaches the administration of a fatty acid ***derivative***, not a fatty acid, and teaches delivery at ***very low doses***, typically an oral dose of 1 mg/kg (assuming a 70 kg adult, a ***70 mg dose***). This low dose is not arbitrarily selected by Ueno. Instead, the very low dose is selected by Ueno to avoid unwanted effects of high dosages of fatty acids. Specifically, Ueno states:

> The present inventor found that at ***an amount as low as that does not induce any conjunctival hyperemia***, a

> fatty acid derivative may improve hypolacrimation, improve basal tear secretion which is not affected by a stimulant, and improve the dry-eye conditions. (column 4, lines 14-21, emphasis added)

It would be of little use to ameliorate dry eye only to cause red, bloodshot eyes as a side effect of the high dose of therapeutic agents given.

Yano is directed to tissue culture methods and can provide no teachings in relation to appropriate dosage levels. However, if Yano could be understood to provide teachings relevant to dosage levels, Yano must be understood to teach the benefit of low doses of the components of the instantly claimed formulations. Specifically, in the first column on page 1100, Yano teaches:

> We observed that DHA, EPA, and AA exhibited cytotoxicity when these fatty acids were added to the culture at high amounts compared with BSA or serum protein levels (data not shown).

References must be considered as a whole (see, e.g., *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). When one reference teaches that a compound should be delivered at relatively a high dose, and another reference teaches that a compound should be delivered at a low dose, the references cannot be properly combined. Alternatively, the references cannot be understood to teach anything regarding appropriate dosages of the compound. ***The teachings of Ueno discourage and discredit the teachings of Troyer.*** Ueno teaches that the dosages of Troyer result in unwanted side effects. This prevents the combination of the references, particularly in regard to the teaching of specific dosages for administration such as those instantly claimed.

The Troyer reference, which teaches the use of a water soluble antioxidant, teaches away from the instantly claimed invention. The water soluble antioxidant, preferably Vitamin C, is included for its physiological activity, not as a preservative. Specifically, Troyer states:

> ***Vitamin C is required for the conversion of dihomo-gamma-linolenic acid into prostaglandin E1***, and

> thus is critical for tear production. Ascorbic acid in tears serves an anti-flammatory role in the eye's defense system. Vitamin C could be replaced by another water-soluble antioxidant, but vitamin C is preferred. (col. 4, ln, 22-27, emphasis added)

Therefore, despite the suggestion of the Office Action, based on the teachings of the cited art, one of skill in the art would not substitute a non-water soluble antioxidant for the water soluble antioxidant taught by Troyer as it would not have the same physiological activity. Schneider does teach that

> Antioxidants may be added to compositions of the present invention to protect the HETE salts from oxidation during storage. Examples of such antioxidants include, but are not limited to, vitamin E and analogs thereof, ascorbic acid and derivatives, and butylated hydroxyanisole (BHA). (col. 9, ln. 18-22)

As preservatives, Schneider may suggest the equivalence of vitamin C and vitamin E, however, ***an obviousness rejection requires some motivation to modify the teachings of Troyer based on the teachings of Schneider to provide the instantly claimed invention***. Applicant submits that there can be no suggestion from Schneider to modify Troyer to substitute a non-water soluble antioxidant for the water soluble antioxidant taught.

Yano does teach the use of vitamin E with DHA, but questions the benefit of inhibiting apoptosis, that is, the benefits of administering vitamin E with DHA. Yano states:

> At the present time, it is unclear whether apoptosis induced by various stimuli is harmful or beneficial in various physiological and pathological circumstances….. [I]t has been reported that caspase inhibitors [which prevent apoptosis] can protect against ischemia of the liver [citation omitted] and brain [citation omitted]. (last paragraph of Yano)

Further, Yano teaches that water soluble antioxidants, including n-acetylcysteine and 2-mercaptoethanol "added to the cell culture simultaneously with TNF and CHI significantly inhibited TNF-induced apoptosis" (second to last paragraph Yano). This is

in contrast to vitamin E that needed to be added to the cells 24 hours prior to TNF to reduce apoptosis. Therefore, one of skill in the art, taking Yano as a whole, in view of the teachings of Troyer and Schneider, would select a water soluble antioxidant, not a non-water soluble antioxidant as claimed.

The modification of the teachings of a reference to make it unsatisfactory for its intended purpose cannot be obvious. Exchanging a water soluble antioxidant for a non-water soluble antioxidant would be contrary to the intended purpose of the Troyer reference. Therefore, such a modification cannot be obvious. Neither Schneider nor Yano teach any advantage of the use of a non-water soluble antioxidant. As noted above, *KSR* did not abrogate the need for some motivation to combine the references to arrive at the claimed invention. Although references teaching specific components of the invention can be combined for reasons different than motivated the inventor to combine the components, references cannot be combined in a manner contrary to the teachings within the references themselves.

Applicant notes that Troyer also teaches that her formulation requires the inclusion of Vitamin A (to treat Vitamin A deficiency, col 2, ln 30; and to regulate proliferation and differentiation of corneal epithelial cells and preserve conjunctival goblet cells, col. 4, ln 29-31) and preferably magnesium (an essential micronutrient, col. 4, ln. 54-55).

Claims 33-37 of the instant application are drawn to compositions “consisting essentially of” the specific formulations recited. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not ***materially*** affect the ***basic*** and ***novel*** characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original) Troyer states that Vitamin A has a physiological activity. The compositions of claims 33-37 do not include Vitamin A which, by the teachings of Troyer, must be understood to have a material effect on the composition of Troyer. It cannot be obvious based on the teachings of Troyer, alone or in combination with any

of the other cited references, to provide a composition that ***does not include Vitamin A***.

Withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If a telephone conference would expedite allowance of this application, the Examiner is urged to call the undersigned.

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Respectfully submitted,

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